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The present Supplemental Arguments are filed concurrently with the filing of a Request for Continued Examination (RCE). Along with Applicant's Response to Final Office Action a Notice of Appeal was mailed on March 25, 2002 and received in the U.S. Patent and Trademark Office (USPTO) on March 29, 2002. The RCE is accompanied by a request for a four-month extension of time, accordingly, the RCE and the present Supplemental Arguments are timely filed.

According to the Advisory Action mailed on May 21, 2002, Applicant's argument were considered but did not place the application in condition for allowance, since they were "with regards to the sole rejection under 35 USC 103 . . . substantially the same as those earlier presented in Paper No. 10."

Applicant disagrees. First of all, in the Response to Final Office Action Applicant, for the first time, made detailed arguments as to why the combination of the Caras and Wang *et al.* references was legally improper. The Examiner did not address these arguments in the Advisory Action. Secondly, Applicant submitted detailed new technical arguments showing that the combination of Caras and Wang *et al.*, even if the two references could be properly combined,

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would not make obvious the invention claimed in the present application. Accordingly, Applicant's arguments submitted in response to the final rejection can be hardly characterized as "substantially the same as those earlier presented." The arguments were the same only in the sense that Applicant maintained the position that the claimed invention was patentable over the cited combination of references. Since Applicant did submit new legal and technical arguments in response to the final Office Action, those arguments deserve consideration on the merits along with the Supplemental Arguments submitted herein.

*The Combination of Caras and Wang et al. is Legally Improper*

As discussed in Applicant's response to the final Office Action, Caras concerns AL-1 neurotrophic factor, which has later been renamed as ephrin-A5, and binds to EphA receptors. Wang *et al.* relates to ephrin-B2 binding to the EphB4 receptor. As discussed in Applicant's earlier arguments, EphA and EphB receptors are fundamentally different, and are recognized as such by those skilled in the art. At present, there are 15 Eph receptors and 9 ephrin ligands known in the art, which are classified into two major subclasses. EphA receptors bind GPI-anchored ephrin-A ligands, while EphB receptors bind ephrin-B ligands, which possess a transmembrane domain and short cytoplasmic region. Caras has no disclosure whatsoever indicating that ephrin-A5 would be structurally or functionally analogous or similar to any ephrin-B, such as ephrin-B2. Inversely, Wang *et al.* has no disclosure whatsoever indicating that ephrin-B2 would be structurally or functionally analogous or similar to any ephrin-A, such as ephrin-A5. Since ephrins-A and -B have been recognized in the art as two different and distinct classes of ephrins, and further since the cited references themselves provide no motivation for their combination, the combination of Caras and Wang *et al.* is legally improper. As the Examiner failed to establish a *prima facie* case of obviousness, the burden to make a showing of non-obviousness has not shifted to the Applicant. For this reason alone, the rejection under 35 U.S.C. § 103 should be withdrawn.

*The Combination of Caras and Wang et al. Does not Make Obvious the Claimed Invention*

Even if the combination of Caras and Wang *et al.* were legally proper, as it is not, the combination would not make obvious the invention claimed in the present application.

Caras concerns ephrin-A5 and discloses, among other things, ephrin-A5 (AL-1) promotes or enhances angiogenesis by receptor activation on endothelial or stromal cells, and finds utility

in wound healing (page 25, line 26 - page 26, line 16). Caras further teaches that ephrin-A5 (AL-1) antagonists find use in inhibiting, preventing, or treating pathological angiogenesis, such as angiogenesis during tumor vascularization (page 29, lines 6-14). Caras has no disclosure, or suggestion indicating that ephrin-A5 would play a role during embryonic development, or, in particular, that ephrin-A5 and its receptor(s) would be expressed on developing arteries and veins, respectively, and communicate with each other to assure proper development of vasculature.

Wang *et al.* report findings indicating that ephrin-B2, present on developing arteries during embryonic development communicates with its receptor, EphB4, present on developing veins. This process appears to be a fundamental interaction for the development of the embryo. If it fails to occur, embryonic development is blocked and the embryo dies at an early stage of development. Wang *et al.* has no evidence of the involvement of ephrin-B2/EphB4 in vascularization at a non-embryonic stage, and has no disclosure suggesting that antagonists of an EphB receptor, such as EphB4, would inhibit angiogenesis in mammals.

In view of fundamental differences between the structure and function of the respective receptors of the Eph A and Eph B subclasses, and ephrin-A5 and ephrin-B2 in particular (as evidenced by the cited disclosures), at the time the present invention was made one skilled in the art would not have been motivated to apply the teaching of Caras *et al.* (which is specific to ephrin-A5) to the teaching of Wang *et al.* (which is specific to ephrin-B2). Furthermore, even if such motivation existed, one of ordinary skill would not have expected that EphB antagonists could inhibit angiogenesis in a mammal, especially in a fully developed mammal, with a reasonable expectation of success.

As noted in Applicant's prior response, a proper obviousness analysis requires the consideration of (1) whether the references themselves or the prior art as a whole had any suggestion of combining the teaching of the references relied upon in the rejection; (2) whether the combination would have suggested to those of ordinary skill in the art that they should make the claimed invention; and (3) whether the combination would also have revealed that those of ordinary skill would have a reasonable expectation of success. In the present case, the answer to all three questions is negative. Only hindsight combination of elements present in the prior art,

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using the teaching of the present invention as a link, could create the impression of obviousness, which is, of course, legally impermissible.

For the foregoing reasons, and the reasons set forth in Applicant's response to the final Office Action, the Examiner is respectfully requested to reconsider and withdraw the present rejection. Should the Examiner maintain the rejection, he is requested to specifically address all arguments made by Applicant, instead of summarily dismissing them, in order to supply a better understanding of issues that can be presented on appeal.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: September 4, 1999

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